HUMAN MONOCLONAL ANTIBODIES TO A NEW UNIVERSAL INFLUENZA A HEMAGGLUTININ HEAD DOMAIN EPITOPE

PRIORITY CLAIM

[0001] This application is a national phase application under 35 U.S.C. § 371 of International Application No. PCT/US2019/047606, filed Aug. 22, 2019, which claims benefit of priority to U.S. Provisional Application Ser. No. 62/721,675, filed Aug. 23, 2018, and U.S. Provisional Application Ser. No. 62/848,301, filed May 15, 2019, the entire contents of each of which are hereby incorporated by reference.

STATEMENT REGARDING FEDERALLY FUNDED RESEARCH

[0002] This invention was made with government support under grant number U19 AI117905 and contract HHSN272201400024C awarded by the National Institutes of Health. The government has certain rights in the invention.

FIELD OF THE DISCLOSURE

[0003] The present disclosure relates generally to the fields of medicine, infectious disease, and immunology. More particular, the disclosure relates to human antibodies binding to a previously unrecognized epitope in the head domain of influenza A hemagglutinin, the novel epitope recognized by such antibodies, and methods of use therefor.

BACKGROUND

[0004] The hypervariable influenza A virus (IAV) has been a primary cause of respiratory illnesses in the human population for centuries. Currently, IAV strains from subtypes H1N1 and H3N2, as well as influenza B viruses, are in human circulation and cause seasonal epidemics. Additionally, other zoonotic IAVs with H1, H3, H5, H6, H7, H9 and H10 HAs have caused sporadic outbreaks of human infections, some with exceedingly high morbidity and mortality rates (Freidl et al., 2014; Neumann and Kawaoka, 2015). Seasonal influenza vaccines are available, but due to the immense variability and continuous mutations in influenza viruses, current vaccines provide protection only against close isolates of the vaccine strains and, therefore, needs to be updated annually, according to predictions of which viruses will be next in circulation (Carrat and Flahault, 2007). Poor matches of the predicted vaccine strains with drifted seasonal viruses can lead to severe influenza seasons (Bridges et al., 2000; Carrat and Flahault, 2007; Nordin et al., 2001). More unpredictably, new influenza viruses emerging from genomic reassortment with drastically altered antigenicity can cause global pandemics. For instance, during the 2009 global pandemic influenza season, a new H1N1 lineage, from reassortment of a variety of avian, pig and human viruses, infected 10-21% of the world population and caused over half a million deaths (Dawood et al., 2012; Shrestha et al., 2011). Hence, investigation of how the immune response can counteract the ever-changing nature of influenza is of great importance for the development of new vaccines and therapeutics.

[0005] The hemagglutinin of influenza is one of the two main glycoproteins on the viral surface and a major target of neutralizing antibodies. Based on structure and antigenicity, there are eighteen defined subtypes (H1-H18) of IAV HAs belonging to two broad groups (Nobusawa et al., 1991; Russell et al., 2004; Tong et al., 2013). Influenza HA consists of an antigenically variable globular head domain containing the receptor-binding site (RBS) for viral attachment and a more conserved stem domain that mediates fusion of viral and cell membranes in the endosome (Carr and Kim, 1993; Weis et al., 1988; Wilson et al., 1981). The HA head domain is the immunodominant domain of the protein and is the target of most antibody responses induced by IAV vaccine or infection (Altman et al., 2015; Angeletti et al., 2017; Caton et al., 1982; Das et al., 2013; Gerhard et al., 1981). However, due to the high level of sequence and antigenic diversity occurring in the HA head domain and the incorporation of large number of glycans in this region to evade immune recognition, most head domain specific antibodies exhibit a very narrow breadth of protection.

[0006] Nonetheless, two classes of broadly neutralizing antibodies (bnAbs) against influenza HA have been discovered previously (Julien et al., 2012; Laursen and Wilson, 2013). The stem-targeted bnAbs, such as the murine monoclonal antibody (mAb) C179, human mAbs CR6261, F10 and A6, are the first class of antibodies found to have broad and heterosubtypic activities, some of which can target nearly all strains of HA across various subtypes and subgroups, e.g., CR9114, MEDI8852 (Corti et al., 2010; Corti et al., 2011; Dreyfus et al., 2013; Dreyfus et al., 2012; Ekiert et al., 2009; Ekiert et al., 2011; Friesen et al., 2014; Joyce et al., 2016; Kallewaard et al., 2016; Kashyap et al., 2008; Kashyap et al., 2010; Lang et al., 2017; Okuno et al., 1993; Smirnov et al., 1999). These bnAbs recognize the highly conserved stem region and block the viral fusion machinery. As a class, anti-stem antibodies tend to be less potent in virus neutralization assays in comparison to RBS-specific antibodies, but stem antibodies often also possess the ability to interact with FcγR on effector cells to mediate antibody-dependent cellular cytotoxicity (ADCC) and protection in vivo (Corti et al., 2011; DiLillo et al., 2016; DiLillo et al., 2014; He et al., 2015). These findings have led to the development of several stem-based immunogens for the purposes of "universal" influenza vaccination (Impagliazzo et al., 2015; Nachbagauer et al., 2016; Valkenburg et al., 2016; Yassine et al., 2015). However, inducing broad-spectrum stem antibodies through vaccination may be challenging due to reduced accessibility of this region on the viral surface and/or reduced immunogenicity.

[0007] A second class of bnAbs targeting the HA head domain also has been discovered (Ekiert et al., 2012; Hong et al., 2013; Joyce et al., 2016; Lee et al., 2014; Lee et al., 2012; Thornburg et al., 2016; Whittle et al., 2011; Xu et al., 2013; Yoshida et al., 2009; Zhu et al., 2013). Most of these head-targeted bnAbs recognize the relatively conserved RBS and block viral attachment and entry. Unlike stem-targeted bnAbs, which generally have heterosubtypic activities, the head-targeted bnAbs tend to have more restricted patterns of recognition within a subtype; for example, the H1-specific CH65, 5J8, and H2-specific 8M2 antibodies (Laursen and Wilson, 2013; Lee et al., 2014; Schmidt et al., 2015; Thornburg et al., 2016; Whittle et al., 2011; Xu et al., 2013). A few exceptions are CO5, F045-92 and S139/1 that can react with the HA head domain from more than one HA subtype (Ekiert et al., 2012; Lee et al., 2014; Lee et al., 2012; Yoshida et al., 2009). However, their heterosubtypic activi-